



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Youmin Shu et al.

Examiner: Janet L. Andres

Serial No.: 09/971,708

Group Art Unit: 1646

Filed: October 9, 2001

Title: Human EphA6 Gene And Polypeptide

BRIEF ON APPEAL

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Commissioner for Patents

P.O. Box 1450

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Sir:

Further to the Notice of Appeal filed September 14, 2004, herewith are three copies of Appellants' Brief on Appeal. The attached check includes the statutory fee for the filing of this Brief and any necessary extension fee.

This is an appeal from the decision of the Examiner rejecting Claims 22-24 of the above-identified application.

(1) REAL PARTY IN INTEREST

The real party in interest in the present application is OriGene Technologies, Inc. An assignment will be filed in due course.

(2) RELATED APPEALS AND INTERFERENCES

There are no known related appeals or interferences.

(3) STATUS OF THE CLAIMS

Claims 1, 3-7, 9-20, and 22-24 are pending in the present application. Claims 1, 3-7, and 9-20 were withdrawn from consideration. Claims 22-24 are on appeal.

(4) STATUS OF AMENDMENTS AFTER FINAL

Not applicable - no amendments filed after final.

(5) SUMMARY OF THE INVENTION

Applicants have described a protein tyrosine kinase that has exquisite tissue specificity, e.g., for brain and pancreas tissues. See, Fig.1 of the specification. The gene was originally known as KSE132, but was classified as a member of the ephrin receptor family – EphA6 – because of its high degree of homology with the same mouse gene. See, Specification, Page 2, line 14. Ephrins, play functional roles during development, especially in pattern formation and morphogenesis. Consistently, EphA6 is present in neural stem cells, and its mouse homolog is expressed during cochlear development. See, Specification, Page 2, lines 29-31.

(6) ISSUES

It is believed that the sole issue in this Appeal is whether Claims 22-24 have utility under 35 U.S.C. §101. The claims are also rejected under 35 U.S.C §112, first paragraph, but this rejection is based on the alleged lack of utility, and therefore is not separately addressed.

In the Office action dated June 14, 2004, it was explained: “The rejection of claims 22-24 under 35 U.S.C. §112, first paragraph, as lacking enablement because the invention lacks utility, is maintained for reasons of record in the office action of 5 January 2004.” However, this Office action did not provide any additional express reasons for the rejection. Thus, if the utility rejection is overturned, it is believed that the 35 U.S.C. §112, first paragraph rejection would be dropped.

(7) GROUPING OF THE CLAIMS

For the purpose of this appeal, Claims 22-24 are considered to stand or fall together.

(8) APPELLANTS' ARGUMENTS

Claims 22-24 have an adequate utility that conforms to the statutory requirements of 35 U.S.C. §101. There are at least three independent bases for utility that can be identified:

1) Well-established utility of ephrins

Ephrins are members of a recognized family of signaling molecules that are involved

in a number of important physiological and developmental processes. In a search of the Medline database, 546 different articles were identified that contained the term “ephrin.” See, Exhibit 1. Ephrins are also described in at least 23 issued patents and 160 published patent applications. See, Exhibit 2.

Very clearly, ephrins comprise a “well-known” class of molecules that are widely used by the scientific community. As indicated in the specification, the claimed ephrin subtype – EphA6 – is a tyrosine kinase receptor. Applicant explained its importance on Page 2 of the specification: “Eph receptor tyrosine kinases and their ligands, ephrins, play functional roles during development, especially in pattern formation and morphogenesis. They are involved in a variety of developmental processes, including, e.g., cell adhesion, retinocollicular mapping, synapse formation, and in the organization of the peripheral vestibular system. See, e.g., Matsunaga et al., Eur. J. Neurosci., 12:1599-1616, 2000; Klein, Current Opinion in Cell Biology, 13:196-203, 2001.” A well-established utility is adequate to satisfy the utility requirements. See, e.g., Revised Utility Guidelines Training Materials, Page 7.

In responding to this argument, the examiner has provided no evidence to rebut the positions that ephrins have a well-established utility and are generally recognized as useful, but instead has chosen to create her own standard of what is sufficient to meet the requirements of §101. As indicated above, ephrins have at least functional roles in differentiation. According to the examiner “That ephrins, generally, are somehow associated in various process of differentiation does not teach the artisan how to use this particular ephrin or a method of identifying it. “ First, the specification clearly teaches how to identify it. Specific nucleotide sequence, polypeptide sequences, and methods of obtaining them are disclosed. See, e.g., Specification, Page 15, line 4. Secondly, the application describes how to use the ephrin protein as a marker for pancreatic cells. See, e.g., Specification, Page 24, line 29; Page 28, line 25. Indeed, this is what is claimed.

It is not necessary to show disease association, as alleged on Page 4 of the Office action dated June 14, 2004. This is a red herring. Disease association is not required by statute, nor is it the only means by which utility can be established. The question is what has applicant provided, and why is that not sufficient to obtain a patent, not what applicant has not disclosed in the specification.

Moreover, Applicants do provide specific information about the differentiation process involving EphA6. On Page 2, lines 30-31, of the specification, it is stated: “EphA6

has also been detected in the developing and adult cochlea. Lee et al., DNA Cell. Biol., 15:817-825, 1996.” (The publication refers to murine EphA6.) It is reasonable to infer that EphA6 would be involved in the same developmental process. (Compare Example 6 of the “Synopsis of Application of Written Description Guidelines.” EphA6 is analogous to the glial example in the Guidelines.)

2) Kinase activity

As indicated in the specification, EphA6 is a tyrosine kinase. See, e.g., Specification, Page 2, lines 15-20. Tyrosine kinase activity can be measured routinely, e.g., as described on Page 4, line 10-Page 5, line 11 of the specification. For example, EphA6 can be used to label substrates with radioactive phosphorus for use in assays.

Enzyme activity is adequate to satisfy the utility requirements. See, e.g., Revised Interim Utility Guideline Training Materials, Example 8, Page 45, under section titled “Analysis,” subheading “1).” Consistently, the Federal Circuit in *Cross v. Iizuka*, 753 F.2d 1040, 224 USPQ 739 (Fed. Cir. 1985), held that an in vitro pharmacological activity for thromboxane synthetase (an enzyme) was sufficient to satisfy the requirements of 35 U.S.C. §101. See, also, M.P.E.P. 2107.01. Thus, knowledge that EphA6 is a tyrosine kinase is a credible, specific, and substantial utility.

Contrary to the examiner’s allegations, ephrin receptors have a characterized tyrosine kinase activity. For example, an activity of this receptor type is described on Page 2 of the specification: “Eph receptors behave similarly to other tyrosine kinase receptors, i.e., binding of the ephrin ligand causes receptor dimerization and trans-phosphorylation by the cytoplasmic kinase domains of two receptor molecules (Klein, Current Opinion in Cell Biology, 13:196-203, 2001).” Thus, at least one of its substrates is known – itself – and this specificity could be used to design other substrates, e.g., peptide fragments of EphA6 containing tyrosine residues.

3) Tissue specificity

The present application discloses that EphA6 is highly restricted to the brain, pancreas, and testis. See, Specification, Fig. 1, and Page 2, lines 26-31. The other cell types in which it is expressed (i.e., brain and testis) do not detract from its utility as a tissue marker, e.g., as a pancreas marker. The pancreas is in the somatic compartment which is distinct from the reproductive compartment (e.g., testis) and the blood-brain barrier. (In females, the testis

cross-reactivity would not be an issue.) For instance, in a patient with pancreatic cancer, it can be used to detect metastatic pancreatic cells, e.g., when metastasis from a primary pancreatic tumor site has occurred, or in a biopsy of the pancreas to identify the pancreatic tissue. See, e.g., Specification, Page 33, lines 1-10; Page 24, beginning on line 29. The examiner has not provided any reasonable basis on which to doubt these assertions.

The Patent Office has rejected applicant's showing of tissue specificity, stating that it is not specific to the molecule. It appears that the Patent Office is now applying a *per se* rule, without reviewing the specific facts of the case, and without properly having solicited Notice and Comment. Furthermore, as explained below, it is failing to follow its own published guidelines reasonably relied upon by Applicant.

Tissue-specificity was published by the Patent Office as adequate to conform to the statutory requirements to get a patent. Example 12 of the Revised Interim Utility Guidelines Training Materials is of a marker that is specific for a cancer – which is a type of tissue specificity. There is no reason why tissue specificity to normal tissue would not analogously satisfy the utility requirements. On Page 4 of the Office action dated June 14, 2004, the examiner attempts to distinguish the cancer example by stating: “This differential expression is a specific property of that protein ...” However, the exact same statement can be made about EphA6: its differential expression in brain and pancreas is a specific property of it. The Patent Office rules are being applied unequally and unfairly.

Secondly, Example 6 in the Synopsis of Application of Written Description Guidelines described a “glial specific G-coupled protein receptor whose function is associated with glial differentiation.” See, attached Pages 278-29. Indeed, this is an example of specificity for a normal tissue. There is no indication in the example that the claim was deficient on any other §112, first paragraph, ground. If it were, it would have been entirely misleading and disingenuous of the Office not to have brought this to patent practitioners' attention.

In responding to Applicant's reliance on Example 6 of the Guidelines, the examiner stated on Page 4:

However, the protein is glial specific and associated with glial cell differentiation, unlike the instant protein, which is not specific to pancreas or any other tissue and is not known to function in pancreatic differentiation. In addition, the exemplified protein was found to be useful to identify agents that regulated differentiation and that thus would be of interest as therapy for gliomas; no such specific utility could be inferred from the general statement that ephrins are

involved in development.

In fact, the specification in the PTO's Example 6 did not provide direct evidence that the glial cell marker was involved in differentiation. It was based solely on homology.

The specification describes an isolated cDNA fragment (SEQ ID NO: 1, a 100mer) obtained from a human glioblastoma cDNA library. SEQ ID NO: 1 is asserted to be homologous to a known DNA molecule that encodes the extracellular domain of a glial specific G-coupled protein receptor whose function is associated with glial cell differentiation. The observed homology is sufficient to support a conclusion that SEQ ID NO: 1 would be glial specific. Further, it would be reasonable to infer that a G-coupled protein receptor encoded by a cDNA that comprised SEQ ID NO: 1 would be involved in the regulation of glial cell differentiation.

There was no disclosure of what specific process of differentiation or development pathway the partial cDNA was involved in, e.g., did it involve interactions with other glial cells? interactions with neurons? the myelination processes? at what temporal stage was the alleged marker was expressed?

Moreover, it was accepted by the PTO that it was "reasonable" to infer utility based on *homology* to a different, but homologous, gene. Along these same lines, on Page 2, lines 30-31, of the specification, it is stated: "EphA6 has also been detected in the developing and adult cochlea. Lee et al., DNA Cell. Biol., 15:817-825, 1996." This reference described the mouse homolog. Using the PTO's own reasoning, it would be reasonable to infer that the human EphA6 described in the application would have the same function.

The Utility and Written Description guidelines were issued by the Patent Office to provide direction to both the examining group and the public in how to interpret the statutory requirements to get a patent. Applicant's claimed invention has a utility that precisely meets the standards set forth in the PTO's own published guidelines. It is obvious that the Patent Office is now applying a double-standard.

On Page 5 of the Office action dated June 14, 2004, it was stated:

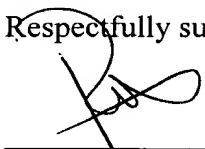
In addition, all that is provided are PCR results showing message regulation. This is not sufficient guidance to allow the skilled artisan to predict that sufficient protein would be expressed and could be identified in pancreatic cells, including metastatic pancreatic cells, and not in stem cells.

The examiner has not provided a reasonable scientific basis to question statements in the specification that EphA6 polypeptide can be used as a marker for pancreas and brain tissue. As stated on Page 468 of the attached page (Exhibit 3) from the *Molecular Biology of the Cell*, "transcription (transcriptional control) usually predominates" in "the pathway from RNA to protein," leading to the reasonable expectation that expression of RNA would lead to production and expression of the protein it encodes. (This same deficiency could have been pointed out in Example 6 of the Written Description Guidelines, but it was not – further supporting Applicant's position that it is reasonable to infer protein expression from DNA expression.)

9) CONCLUSION

Reversal of the rejection is therefore mandated by law, and is respectfully and courteously requested.

Respectfully submitted,



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Attorney Docket No.: ORIGEN-0016

Date: September 14, 2004

APPENDIX

22. A method of determining the presence in pancreas cells of a polypeptide coded for by KSE132, comprising

contacting a sample comprising pancreas cells with an antibody which is specific for a polypeptide coded for by KSE132 having the amino acid sequence set forth in SEQ ID NO 2 under conditions effective for said antibody to specifically bind to said polypeptide, and

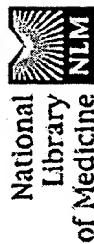
detecting the binding of said antibody to said polypeptide, whereby the presence in pancreas cells of said polypeptide is determined.

23. A method of claim 22, wherein said detecting is performed by immunofluorescence, Western blot, radioimmunoassay, enzyme-linked-immunoabsorbent assay, or enzyme immunoassay.

24. A method of claim 22, wherein said antibody is specific for amino acids 1-23, 24-538, or 834-1036 of SEQ ID NO 2.



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☐ 1: Ikegami R, Zheng H, Ong SH, Culotti J.



Integration of Semaphorin-2A/MAB-20, ephrin-4, and UNC-129 TGF-beta Signaling Pathways Regulates Sorting of Distinct Sensory Rays in *C. elegans*.
Dev Cell. 2004 Mar;6(3):383-95.
PMID: 15030761 [PubMed - in process]

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☐ 2: Zhang HM, Cheng HH.



SNP identification and genetic mapping of chicken ephrin type-B receptor 2 gene to linkage group E54.
Anim Genet. 2004 Apr;35(2):162-3. No abstract available.
PMID: 15025591 [PubMed - in process]

Related Articles, Links



☐ 3: Chiarugi P, Taddei ML, Schiavone N, Papucci L, Giannoni E, Fiaschi T, Capaccioli S, Raugei G, Ranponi G.



LMW-PTP is a positive regulator of tumor onset and growth.
Oncogene. 2004 Mar 15 [Epub ahead of print]
PMID: 15021900 [PubMed - as supplied by publisher]

Related Articles, Links



☐ 4: Williams SE, Mason CA, Herrera E.



The optic chiasm as a midline choice point.
Curr Opin Neurobiol. 2004 Feb;14(1):51-60.
PMID: 15018938 [PubMed - in process]

Related Articles, Links



☐ 5: Patan S.




Vasculogenesis and angiogenesis.
Cancer Treat Res. 2004;117:3-32.
PMID: 15015550 [PubMed - in process]

Related Articles, Links



☐ 6: Feldheim DA, Nakamoto M, Osterfield M, Gale NW, DeChiara TM, Rohatgi R, Yancopoulos GD, Flanagan JG.

Related Articles, Links

 Loss-of-function analysis of EphA receptors in retinotectal mapping.

J Neurosci. 2004 Mar 10;24(10):2542-50.
PMID: 15014130 [PubMed - in process]

 7: Chen ZY, Sun C, Reuhl K, Bergemann A, Henkemeyer M, Zhou R.

Related Articles, Links

 Abnormal hippocampal axon bundling in EphB receptor mutant mice.


J Neurosci. 2004 Mar 10;24(10):2366-74.
PMID: 15014111 [PubMed - in process]

 8: Wimmer-Kleikamp SH, Janes PW, Squire A, Bastiaens PJ, Lackmann M.


Related Articles, Links

 Recruitment of Eph receptors into signaling clusters does not require ephrin contact.

J Cell Biol. 2004 Mar 1;164(5):661-6.
PMID: 14993233 [PubMed - in process]

 9: Tanaka M, Ohashi R, Nakamura R, Shimura K, Kano T, Sakai R, Sugimura H.


Related Articles, Links

 Tiam1 mediates neurite outgrowth induced by ephrin-B1 and EphA2.


EMBO J. 2004 Mar 10;23(5):1075-88. Epub 2004 Feb 26.
PMID: 14988728 [PubMed - in process]

 10: Andres AC, Ziemiecki A.


Related Articles, Links

 Eph and ephrin signaling in mammary gland morphogenesis and cancer.


J Mammary Gland Biol Neoplasia. 2003 Oct;8(4):475-85.
PMID: 14985642 [PubMed - in process]

 11: Zisch AH, Zeisberger SM, Ehrbar M, Djonov V, Weber CC, Ziemiecki A, Pasquale EB, Hubbell JA.


Related Articles, Links

 Engineered fibrin matrices for functional display of cell membrane-bound growth factor-like activities: study of angiogenic signaling by ephrin-B2.


Biomaterials. 2004 Jul;25(16):3245-57.
PMID: 14980419 [PubMed - in process]

 12: Irie F, Yanaguchi Y.


Related Articles, Links

 EPHB receptor signaling in dendritic spine development.








Front Biosci. 2004 May 1;9:1365-73.
PMID: 14977552 [PubMed - in process]

 13: Kataoka H, Igarashi H, Kanamori M, Ihara M, Wang JD, Wang YJ, Li ZY, Shimamura T, Kobayashi T, Maruyama K, Nakamura T, Arai H, Kajimura M, Hanai H, Tanaka M, Sugimura H.

Related Articles, Links

 Correlation of EPHA2 overexpression with high microvessel count in human primary colorectal cancer.

Cancer Sci. 2004 Feb;95(2):136-41.
PMID: 14965363 [PubMed - in process]

- ☐ **14:** [Rodger J, Vitale PN, Tee LB, King CE, Bartlett CA, Fall A, Brennan C, O'Shea JE, Dunlop SA, Beazley LD.](#) [Related Articles, Links](#)
 EphA/ephrin-A interactions during optic nerve regeneration: restoration of topography and regulation of ephrin-A2 expression.
 Mol Cell Neurosci. 2004 Jan;25(1):56-68.
 PMID: 14962740 [PubMed - in process]
- ☐ **15:** [Mao W, Luis E, Ross S, Silva J, Tan C, Crowley C, Chui C, Franz G, Senter P, Koeppen H, Polakis P.](#) [Related Articles, Links](#)
 EphB2 as a therapeutic antibody drug target for the treatment of colorectal cancer.
 Cancer Res. 2004 Feb 1;64(3):781-8.
 PMID: 14871799 [PubMed - in process]
- ☐ **16:** [Eberhart J, Barr J, O'Connell S, Flagg A, Swartz ME, Cramer KS, Tosney KW, Pasquale EB, Krull CE.](#) [Related Articles, Links](#)
 Ephrin-A5 exerts positive or inhibitory effects on distinct subsets of EphA4-positive motor neurons.
 J Neurosci. 2004 Feb 4;24(5):1070-8.
 PMID: 14762125 [PubMed - in process]
- ☐ **17:** [Bicknell R, Harris AL.](#) [Related Articles, Links](#)
 Novel angiogenic signaling pathways and vascular targets.
 Annu Rev Pharmacol Toxicol. 2004;44:219-38.
 PMID: 14744245 [PubMed - in process]
- ☐ **18:** [Raza SM, Fuller GN, Rhee CH, Huang S, Hess K, Zhang W, Sawaya R.](#) [Related Articles, Links](#)
 Identification of necrosis-associated genes in glioblastoma by cDNA microarray analysis.
 Clin Cancer Res. 2004 Jan 1;10(1 Pt 1):212-21.
 PMID: 14734472 [PubMed - in process]
- ☐ **19:** [Lai KO, Chen Y, Po HM, Lok KC, Gong K, Ip NY.](#) [Related Articles, Links](#)
 Identification of the Jak/Stat proteins as novel downstream targets of EphA4 signaling in muscle: Implications in the regulation of acetylcholinesterase expression.
 J Biol Chem. 2004 Jan 15 [Epub ahead of print]
 PMID: 14729671 [PubMed - as supplied by publisher]
- ☐ **20:** [Hafner C, Schmitz G, Meyer S, Bataille F, Hau P, Langmann T, Dietmaier W, Landthaler M, Vogt T.](#) [Related Articles, Links](#)
 Differential gene expression of Eph receptors and Ephrins in benign human tissues and cancers.
 Clin Chem. 2004 Mar;50(3):490-9. Epub 2004 Jan 15.
 PMID: 14726470 [PubMed - in process]

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




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- 50 [20030219795](#) [SCDs as modifiers of the p53 pathway and methods of use](#)
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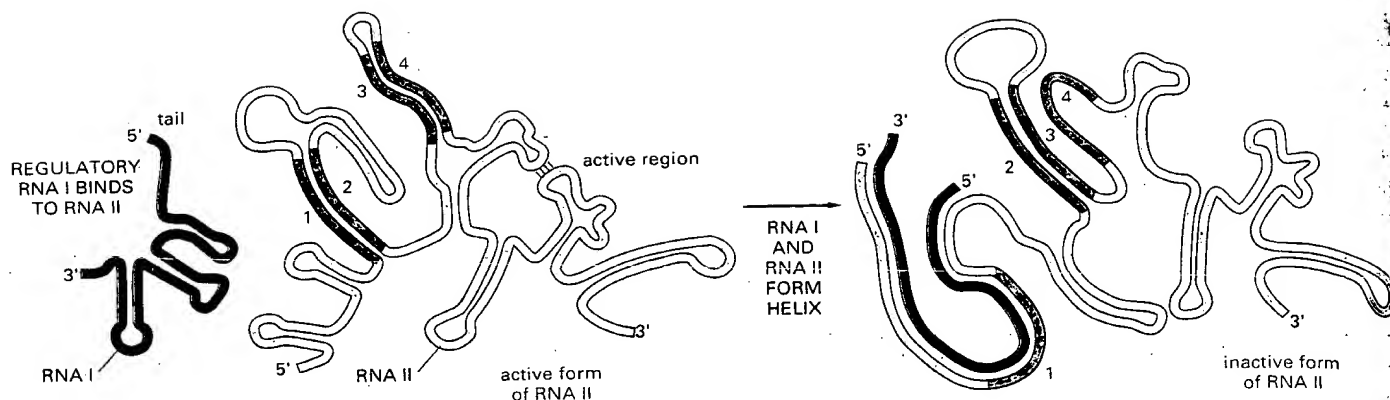
MOLECULAR BIOLOGY OF THE CELL

THIRD EDITION

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accomplished by specialized RNA-binding proteins. In other cases, however, the recognition of specific RNA sequences is carried out by other RNA molecules, which use complementary RNA-RNA base-pairing as part of their recognition mechanism. RNA-RNA pairings, for example, are known to play a central part in translation, in RNA splicing, in several other forms of RNA processing, and in the RNA editing that occurs in trypanosomes. In attempting to dissect posttranscriptional mechanisms, we have largely entered an RNA world.

RNA molecules also have other regulatory roles in cells. The *antisense RNA* strategy for experimentally manipulating cells so that they fail to express a particular gene (see p. 326) mimics a normal mechanism that is known to regulate the expression of a few selected genes in bacteria and may be used much more widely than is now realized. A well-understood example of this kind of mechanism provides a feedback control on the initiation of DNA replication for a large family of bacterial DNA plasmids. The control system limits the number of copies of the plasmid made in the cell, thereby preventing the plasmid from killing its host cell by overreplicating (Figure 9-89).

Studies of RNA-catalyzed reactions are of special interest from an evolutionary perspective. As discussed in Chapter 1, the first cells are thought to have lacked DNA and may have contained very few, if any, proteins. Many of the RNA-catalyzed reactions in present-day cells seem to represent molecular fossils—descendants of the complex network of RNA-mediated reactions that are presumed to have dominated cell metabolism more than 3.5 billion years ago. Recombinant DNA technology has allowed large amounts of pure RNAs of any sequence to be produced *in vitro* with purified RNA polymerases (see Figure 7-36), making it possible to study the detailed chemistry of RNA-catalyzed reactions. From an understanding of many such reactions, biologists hope to be able to trace the path by which a living cell first evolved.

Figure 9-89 Antisense RNA strategy for regulating plasmid numbers in bacteria. A regulatory interaction between two RNA molecules maintains a constant plasmid copy number in the ColE1 family of bacterial DNA plasmids. RNA I (about 100 nucleotides long) is a regulatory RNA that inhibits the activity of RNA II (about 500 nucleotides long), which normally helps initiate plasmid DNA replication. The concentration of RNA I increases in proportion to the number of plasmid DNA molecules in the cell, so that as plasmid numbers increase, plasmid replication is inhibited. RNA I is complementary in sequence to the 5' end of RNA II. In RNA II sequence 2 is complementary to both sequence 1 and sequence 3, and it is displaced from one to the other by the binding of RNA I; RNA I thereby alters the conformation of sequence 4, inactivating RNA II. (After H. Masukata and J. Tomizawa, *Cell* 44:125-136, 1986.)

Summary

Many steps in the pathway from RNA to protein are regulated by cells to control gene expression. Most genes are thought to be regulated at multiple levels, although control of the initiation of transcription (transcriptional control) usually predominates. Some genes, however, are transcribed at a constant level and turned on and off solely by posttranscriptional regulatory processes. These processes include (1) attenuation of the RNA transcript by its premature termination, (2) alternative RNA splice-site selection, (3) control of 3'-end formation by cleavage and poly-A addition, (4) control of transport from the nucleus to the cytosol, (5) localization of mRNAs to particular parts of the cell, (6) RNA editing, (7) control of translational initiation, (8) regulated mRNA degradation, and (9) translational recoding. Most of these control processes require the recognition of specific sequences or structures in the RNA molecule being regulated. This recognition can be accomplished by either a regulatory protein or a regulatory RNA molecule.

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